

Amendments to the Specification:

Please replace the paragraph at page 2, from line 9 through line 14, with the following paragraph:

--In an effort to compensate for the deficiencies of individual thermostable polymerases, a second approach has been to develop multiple enzyme assemblages, combining, for example, Taq polymerase and a proofreading enzyme, such as Pfu polymerase or ~~Vent~~ *Thermococcus litoralis*-derived VENT<sup>®</sup> DNA polymerase. These multiple-enzyme mixtures exhibit higher PCR efficiency and reduced error rates when compared to Taq polymerase alone (Barnes, Proc. Natl. Acad. Sci USA 91:2216-2220 (1994).) --

Please replace the paragraph at page 2, from line 15 through line 22, with the following paragraph:

--Another approach has been to develop new and useful variants of Taq polymerase through deletion/truncation techniques. The Stoffel fragment, for example, is a 544 amino acid C-terminal truncation of Taq DNA polymerase, possessing an enzymatically active 5' 3' polymerase domain but lacking 3'-5'exonuclease and 5'-3' exonuclease activity. Other commercially available thermostable polymerase deletions include ~~Vent~~ *Thermococcus litoralis*-derived VENT<sup>®</sup> (exo-) and ~~Deep Vent~~ Deep Vent<sub>R</sub><sup>TM</sup> (exo-) (New England Biolabs, Beverly, MA). Deletion mutations serve only to remove functional domains of a nucleic acid polymerase, however, and do not add any novel features or enzymatic properties. --

Please replace the paragraph at page 9, from line 1 through line 2, with the following paragraph:

-- In another embodiment, the proofreading polymerase is selected from the group consisting of Pfu, KOD, Tgo, ~~Vent~~ *Thermococcus litoralis*-derived VENT<sup>®</sup> (exo-) and ~~Deep Vent~~ Deep Vent<sub>R</sub><sup>TM</sup>(exo-) (New England Biolabs, Beverly, MA).--

Please replace the paragraph at page 17, line 20, through page 20, line 11, with the following paragraph:

--The nucleic acid polymerases used in the present invention may be mesophilic or thermophilic, and are preferably thermophilic. Preferred mesophilic DNA polymerases

include T7 DNA polymerase, T5 DNA polymerase, T4 DNA polymerase, Klenow fragment DNA polymerase, DNA polymerase III and the like. Preferred thermostable DNA polymerases that may be used in the methods of the invention include Taq, Tne, Tma, Pfu, Tfl, Tth, Stoffel fragment, Vent *Thermococcus litoralis*-derived VENT<sup>®</sup> (exo-) and Deep Vent Deep Vent<sub>R</sub><sup>TM</sup>(exo-) (New England Biolabs, Beverly, MA) DNA polymerases, KOD, Tgo, JDF3, and mutants, variants and derivatives thereof (U.S. Pat. No. 5,436,149; U.S. Patent 4,889,818; U.S. Pat. No. 4,965,18S; U.S. Pat. No. 5,079,352; U.S. Patent 5,614,365; U.S. Pat. No. 5,374,553; U.S. Pat. No. 5,270,179; U.S. Pat. No. 5,047,342; U.S. Pat. No. 5,512,462; WO 92/06188; WO 92/06200; WO 96/10640; Barnes, W. M., Gene 112:29-35 (1992); Lawyer, F. C., et al., PCR Meth. Appl. 2:275-287 (1993); Flaman, J. -M, et al., Nuc. Acids Res. 22(15):3259- 3260 (1994)). For amplification of long nucleic acid molecules (e.g, nucleic acid molecules longer than about 3-5 Kb in length), at least two DNA polymerases (one substantially lacking 3' exonuclease activity and the other having 3' exonuclease activity) are typically used. See U.S. Pat. No. 5,436,149; U.S. Pat. No. 5,512,462; Fames, W. M., Gene 112:29-35 (1992); and copending U.S. patent application Ser. No. 09/741,664, filed Dec. 21, 2000, the disclosures of which are incorporated herein in their entireties. Examples of DNA polymerases substantially lacking in 3' exonuclease activity include, but are not limited to, Taq, Tne(exo- ), Tma(exo- ), Pfu(exo- ), Pwo(exo- ), exo-KOD and Tth DNA polymerases, and mutants, variants and derivatives thereof.--

Please replace the paragraph at page 18, from line 12 through line 26, with the following paragraph:

--As used herein, "archaeal" DNA polymerase refers to DNA polymerases that belong to either the Family B/pol I-type group (e.g., *Pfu*, KOD, Pfx, Vent, Deep Vent, Tgo, Pwo) or the pol II group (e.g., *Pyrococcus furiosus* DP1/DP2 2-subunit DNA polymerase). In one embodiment, "archaeal" DNA polymerase refers to thermostable archaeal DNA polymerases (PCR-able) and include, but are not limited to, DNA polymerases isolated from *Pyrococcus* species (*furiosus*, species GB-D, *woesii*, *abyssii*, *horikoshii*), *Thermococcus* species (*kodakaraensis* KOD1, *litoralis*, species 9 degrees North-7, species JDF-3, *gorgonarius*), *Pyrodictium occultum*, and *Archaeoglobus*

fulgidus. It is estimated that suitable archaea would exhibit maximal growth temperatures of >80-85°C or optimal growth temperatures of >70-80°C. Appropriate PCR enzymes from the archaeal pol I DNA polymerase group are commercially available, including *Pfu* (Stratagene), KOD (Toyobo), Pfx (Life Technologies, Inc.), ~~Vent~~ *Thermococcus litoralis*-derived VENT® (New England BioLabs), and Deep Vent~~Deep Vent~~™(exo-) (New England BioLabs), Tgo (Roche), and Pwo (Roche). Additional archaea related to those listed above are described in the following references: Archaea: A Laboratory Manual (Robb, F.T. and Place, A.R., eds.), Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1995.--

Please replace the paragraph at page 33, from line 6 through line 9, with the following paragraph:

-- N. HMf-like protein- ~~Vent~~ *Thermococcus litoralis*-derived VENT® (New England BioLabs) fusion

O. HMf-like protein- ~~Vent~~ *Thermococcus litoralis*-derived VENT® (New England BioLabs) fusion

P. HMf-like protein- Deep Vent~~Vent~~™(exo-) (New England BioLabs) fusion

Q. HMf-like protein- Deep Vent~~Vent~~™(exo-) (New England BioLabs) fusion--

Please replace the paragraph at page 34, from line 5 through line 8, with the following paragraph:

-- GG. PCNA- ~~Vent~~ *Thermococcus litoralis*-derived VENT® (New England BioLabs) fusion

HH. PCNA- ~~Vent~~ *Thermococcus litoralis*-derived VENT® (New England BioLabs) fusion

II. PCNA- Deep Vent~~Vent~~™(exo-) (New England BioLabs) fusion

JJ. PCNA- Deep Vent~~Vent~~™(exo-) (New England BioLabs) fusion --

Please replace the paragraph at page 35, from line 3 through line 6, with the following paragraph:

-- YY. Sac7d - ~~Vent~~ *Thermococcus litoralis*-derived VENT® (New England BioLabs) fusion

ZZ. Sac7d - Vent Thermococcus litoralis-derived VENT® (New England BioLabs) fusion

AAA. Sac7d - Deep Vent VentR™(exo-) (New England BioLabs) fusion

BBB. Sac7d - Deep Vent VentR™(exo-) (New England BioLabs) fusion--

Please replace the paragraph at page 35, from line 17 through line 20, with the following paragraph:

-- MMM. Sso7D - Vent Thermococcus litoralis-derived VENT® (New England BioLabs) fusion

NNN. Sso7D - Vent Thermococcus litoralis-derived VENT® (New England BioLabs) fusion

OOO. Sso7D - Deep Vent VentR™(exo-) (New England BioLabs) fusion

PPP. Sso7D - Deep Vent VentR™(exo-) (New England BioLabs) fusion --

Please replace the paragraph at page 37, from line 24 through page 38, line 5, with the following paragraph:

-- Thermostable archaeal DNA polymerases are isolated from Pyrococcus species (furiosus, species GB-D, woesii, abysii, horikoshii), Thermococcus species (kodakaraensis KOD1, litoralis, species 9 degrees North-7, species JDF-3, gorgonarius), Pyrodictium occultum, and Archaeoglobus fulgidus. It is estimated that suitable archaea would exhibit maximal growth temperatures of >80-85°C or optimal growth temperatures of >70-80°C. Appropriate PCR enzymes from the archaeal pol I DNA polymerase group are commercially available, including *Pfu* (Stratagene), KOD (Toyobo), Pfx (Life Technologies, Inc.), Vent Thermococcus litoralis-derived VENT® (New England BioLabs), Deep Vent VentR™(exo-) (New England BioLabs), Tgo (Roche), and Pwo (Roche). --

Please replace the paragraph at page 49, from line 7 through line 10, with the following paragraph:

-- A person of average skill in the art having the benefit of this disclosure will recognize that DNA polymerases derived from other exo<sup>+</sup> DNA polymerases including Vent Thermococcus litoralis-derived VENT® (New England BioLabs) DNA polymerase, JDF-3 DNA polymerase, Tgo DNA polymerase, KOD DNA polymerase and the like may be suitably used in the subject compositions. --

Please replace the paragraph at page 54, from line 15 through line 20, with the following paragraph:

-- Three 3' to 5' exonuclease motifs have been identified, and mutations in these regions have also been shown to abolish 3' to 5' exonuclease activity in Klenow, φ29, T4, T7, and ~~Vent~~ *Thermococcus litoralis*-derived VENT® (New England BioLabs) DNA polymerases, yeast Pol α, Pol β, and Pol γ, and *Bacillus subtilis* Pol III (reviewed in Derbyshire et al., 1995, Methods. Enzymol. 262:363). Methods for preparing additional DNA polymerase mutants, with reduced or abolished 3' to 5' exonuclease activity, are well known in the art. --

Please replace the paragraph at page 54, from line 21 through line 27, with the following paragraph:

-- Commercially-available enzymes that lack both 5' to 3' and 3' to 5' exonuclease activities include Sequenase (exo<sup>-</sup> T7; USB), *Pfu* exo<sup>-</sup> (Stratagene), exo<sup>-</sup> ~~Vent~~ *Thermococcus litoralis*-derived VENT® (New England BioLabs), exo<sup>-</sup> Deep ~~Vent~~ Vent<sub>R</sub>™(exo-) (New England BioLabs), exo<sup>-</sup> Klenow fragment (Stratagene), *Bst* (Bio-Rad), Isotherm (Epicentre), Ladderman (Panvera), KlenTaq1 (Ab Peptides), Stoffel fragment (Perkin-Elmer), ThermoSequenase (USB), and TaqFS (Hoffman-LaRoche), any one of which may be used as the non chimeric DNA polymerase component in the blend of the invention disclosed herein.--

Please replace the paragraph at page 60, from line 12 through line 19, with the following paragraph:

-- In another embodiment, the DNA polymerase fusion of the invention comprises a DNA polymerase, or part thereof, that lacks both 5' to 3' and 3' to 5' exonuclease activities including, but not limited to, Sequenase (exo<sup>-</sup> T7; USB), *Pfu* exo<sup>-</sup> (Stratagene), exo<sup>-</sup> Vent (New England BioLabs), exo<sup>-</sup> Deep ~~Vent~~ Vent<sub>R</sub>™(exo-) (New England BioLabs), exo<sup>-</sup> Klenow fragment (Stratagene), *Bst* (Bio-Rad), Isotherm (Epicentre), Ladderman (Panvera), KlenTaq1 (Ab Peptides), Stoffel fragment (Perkin-Elmer), ThermoSequenase (USB), and TaqFS (Hoffman-LaRoche), any one of which may be used as the chimeric DNA polymerase fusion of the invention disclosed herein.--